

### **III. REMARKS/ARGUMENTS**

#### **A. Status of Claims/Specification**

Claims 38 and 47-53 are currently pending. Claims 1-37 and 39-46 were previously cancelled. Claim 38 has been amended without prejudice. The abstract has also been amended herein without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

#### **B. Rejection under 35 U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda**

In the Office Action, the Examiner rejected claims 38, 47-48 and 50-53 under 35 U.S.C. 103 (a) over US 4,569,937 (hereinafter "Baker"), Swingle et al. Drugs Exptl. Clin, Res. Vol. X (8-9) (1984) (hereinafter "Swingle") and/or Rabasseda, Drugs of Today Vol. 32, No. 5 (1996) pages 365-384 (hereinafter "Rabasseda").

##### **1. The Recited Transitional Phrase**

In the Office Action, the Examiner stated that "the transitional phrase 'consisting essentially of' is construed as equivalent to comprising (open) due to lack of clarity in the claims and specification." The Examiner further states that "Applicant argues ... that the claim excludes any analgesic compounds not recited and is limited to only the two recited compounds. However, the claim does not explicitly state a limitation concerning only two active agents. Therefore applicant argues limitations not found in the claims."

In response, the Examiner is directed to claim 38, which has been amended to recite "consisting of" in place of "consisting essentially of." Further, claim 38 has also been amended to specifically recite that the claimed method of treatment utilizing an analgesic compounds consisting of two particular agents (i.e., nimesulide and oxycodone, and/or their respective salts). Applicants further note that the Abstract has been amended to include the term "consisting."

In view of these amendments, Applicants respectfully submit that the previously submitted arguments are not directed to limitations not found in the claims and reconsideration is requested.

## 2. The Baker Reference

In the Office Action, the Examiner cites the Baker reference at column 1, lines 23-25, which states that "[t]his patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone." The Examiner further states that the Baker reference teaches "the entire genus of NSAIDs plus narcotic analgesics..."

Applicants respectfully submit that this passage in Baker is taken outside of context. The statement at column 1, lines 23-35 regarding "this patent" actually refers to U.S. Patent No. 4,464,376 issued to A. Sunshine et al. (hereinafter "Sunshine"). A copy of Sunshine is enclosed herewith as Exhibit A. Applicants submit that the purported invention in Sunshine is directed to combinations of caffeine and NSAIDs; caffeine and narcotic analgesics; and caffeine and NSAIDs/narcotic analgesics. Applicants respectfully submit that the present claims exclude the presence of caffeine by virtue of the "consisting essentially of" terminology in the claims.

Further, contrary to the Examiner's statement, the term "selected NSAIDs" (emphasis added) is not directed to "the entire genus of NSAIDs".

In support of this position, the Examiner's attention is directed to Sunshine at column 14, lines 58-61, which recite "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove.**" (Emphasis added).

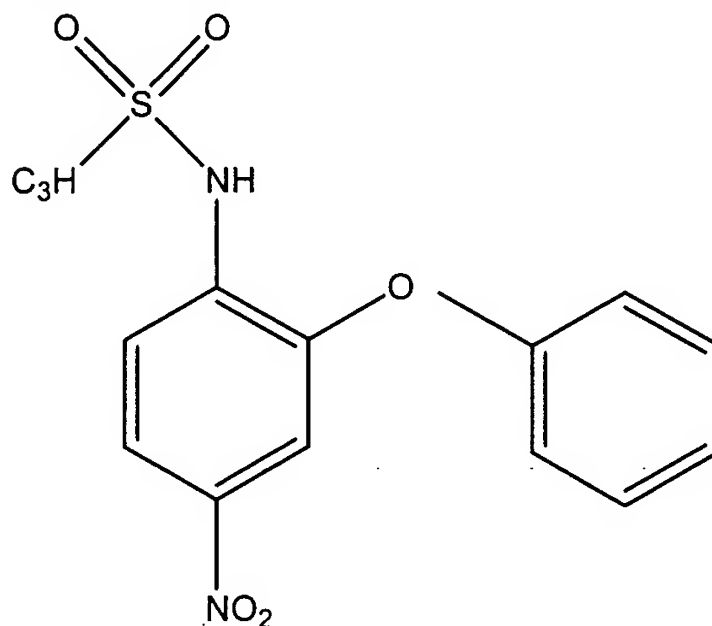
These five categories are set forth at column 7, lines 42-50 of Sunshine which states that:

The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives; and
- (5) the oxicams.

The chemical structures of the (5) categories are exemplified in columns 8-11.

Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* nimesulide:



does not fall within any of the five structural categories indicated above. Therefore, even assuming arguendo that Baker contemplates the use of other NSAIDs based on the reference to Sunshine, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in Sunshine and would not include nimesulide.

Moreover, Applicants submit that Baker teaches away from the use of NSAIDs other than ibuprofen, based on Baker's discussions of the synergistic effect between ibuprofen and narcotic analgesics, and the absolute absence of any reference to other NSAIDs which may be used in the Baker formulation. In further support of this position, the Examiner is respectfully directed to column 1, lines 6 - 9 of Baker which states as follows:

*This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*  
(Emphasis Added)

The Examiner is also directed to column 2, lines 11-15 of Baker which states as follows:

*According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*  
(Emphasis Added)

The following additional passages from Baker are also limited to a combination of narcotic analgesics and ibuprofen:

Column/Lines	Text
Title:	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Abstract:	ABSTRACT Pharmaceutical compositions of narcotic analgesics and ibuprofen . . .
Figure 1	ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN . . .
Col. 1, line 1 & 2	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Col. 2, lines 20-24	. . . synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof . . .
Col. 2, line 34 & 35	. . . various dose ratios of oxycodone and ibuprofen.
Col. 2, lines 64 & 65	In a composition of the invention, oxycodone and ibuprofen are combined . . .
Col. 3, lines 23 & 24	. . . unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen . . .
Col. 3, lines 53-56	. . . the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen.

Column/Lines	Text
Col. 4, lines 24-29	Example 1 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 4, lines 36-42	Example 2 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 300.0
Col. 4, lines 48-55	Example 3 Oxycodone/Ibuprofen Tablets Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 4, lines 60-66	Example 4 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 8-14	Example 5 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 300.00
Col. 5, lines 20-26	Example 6 Oxycodone/Ibuprofen Capsules Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 5, lines 33-39	Example 7 Oxycodone/Ibuprofen Tablets Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 45-51	Example 8 Oxymorphone/Ibuprofen Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 5, lines 58-63	Example 9 Oxymorphone/Ibuprofen Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 1-7	Example 10 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 60.0

Column/Lines	Text
Col. 6, lines 13-19	<p style="text-align: right;">Example 11</p> Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 6, lines 25-31	<p style="text-align: right;">Example 12</p> Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 38-43	<p style="text-align: right;">Example 13</p> Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 6, lines 49-55	<p style="text-align: right;">Example 14</p> Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 6, lines 61-66	<p style="text-align: right;">Example 15</p> Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 9-14	<p style="text-align: right;">Example 16</p> Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 7, lines 21-27	<p style="text-align: right;">Example 17</p> Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 7, lines 33-39	<p style="text-align: right;">Example 18</p> Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 46-51	<p style="text-align: right;">Example 19</p> Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 7, lines 57-63	<p style="text-align: right;">Example 20</p> Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 300.0

Column/Lines	Text
Col. 8, lines 1-7	Example 21 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 13-19	Example 22 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 8, lines 26-31	Example 23 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 37-43	Example 24 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 56-58	All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or oxycodone hydrochloride solutions.
Col. 8, line 62	A stock suspension of ibuprofen is . . .
Col. 9, lines 22-24	Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen . . .
Col. 9, lines 45-47	In order to study the interaction between oxycodone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected.
Col. 10, lines 25 & 26	The synergistic interaction of oxycodone hydrochloride and ibuprofen . . .
Col. 10, lines 29-31	. . . the analgesic effect of oxycodone along is presented in the ordinate, and that of ibuprofen alone is on the abscissa.
Col. 10, lines 32-34	. . . exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1.
Col. 10, lines 35 & 36	. . . representing oxycodone and ibuprofen alone . . .
Col. 10, lines 36-38	. . . representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios.
Col. 11, lines 31-33	. . . straight line additivity hypothesis for oxycodone HCl and ibuprofen . . .
Col. 12, lines 52-54	. . . analgesic synergism is established for all combinations of oxycodone and ibuprofen.
Col. 12, lines 55 & 56	By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone . . .
Col. 12, lines 62 & 63	. . . it is predicted that oxycodone and ibuprofen would demonstrate analgesic potentiation . . .

Column/Lines	Text
Table 1	TABLE 1 ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS Oxycodone    Ibuprofen                      Oxycodone    Ibuprofen
Col. 13, lines 49-55	1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

As evidenced above, ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

Therefore, not only would one of ordinary skill in the art not be motivated to substitute the ibuprofen of the formulations of Baker with nimesulide in view of Swingle and/or Rabasseda, Applicants submit that Baker teaches away from the use of all other NSAIDs other than ibuprofen. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Baker in view of Swingle and/or Rabasseda be removed.

**C. Rejection under 35 U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)**

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al., Swingle et al. and/or Rabasseda in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.)

This rejection is traversed. Applicants respectfully submit that the Oshlack references do not cure the deficiencies of Baker in view of Swingle and/or Rabasseda for the reasons discussed above.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) over Baker, Swingle and/or Rabasseda in view of Oshlack and Oshlack be removed.



IV. **CONCLUSION**

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,

DAVIDSON, DAVIDSON & KAPPEL, LLC

By: 

Robert J Paradiso  
Reg. No. 41,240

DAVIDSON, DAVIDSON & KAPPEL, LLC  
Patents, Trademarks and Copyrights  
485 Seventh Avenue, 14<sup>th</sup> Floor  
New York, New York 10018  
(212) 736-1940